NTP
National Toxicology Program

Host Susceptibility Branch Review

John E. French, Ph.D., Acting Chief

National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors

December 9-10, 2009

Host Susceptibility Initiative

- NTP BSC
  - ✓ June 2006
    - **Concept (Consensus Support)**
  - ✓ December 2006
    - **R&D Contract Concept Proposal (Approved)**
  - ✓ December 2007
    - **Update**
  - ✓ June 2008
    - **HSB Update (Information Exchange)**
  - ✓ **December 2009**
    - **Interim Progress Review**

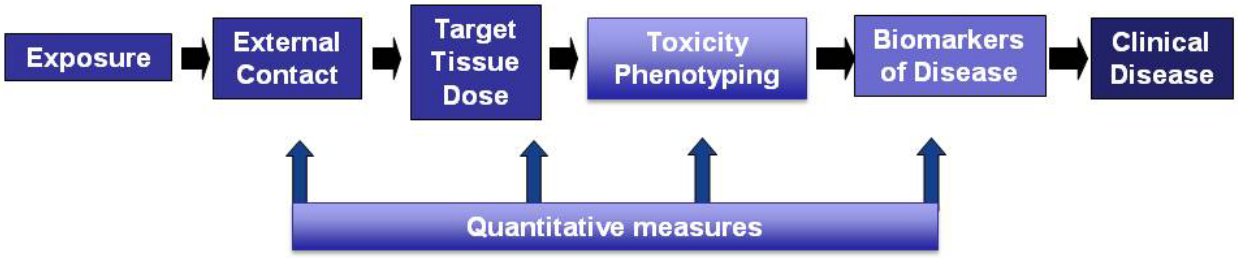
Continued….

- Information Expert Panel July 2006
- Intramural Research Initiative 2006-2007
- Retreats & Workshops
  - NTP Workshop – Strains & Stocks, 16-17 June 2005
  - NTP Retreat, 18-19 October 2006
  - CTC, Braunschweig, Germany May 2007
  - The Toxicology Forum, Aspen, July 2007
  - SOT, Seattle, March 2008 & SLC, March 2010
- NIH Guide & Federal Register RFI 2007; multiple list servers
  - Request for Information on HSI Development
  - 26 In-depth responses from 25 different research institutions

NTP
National Toxicology Program

Genetic and Epigenetic Basis for Susceptibility

ADME – toxicokinetics & toxicodynamics



Point of contact measures

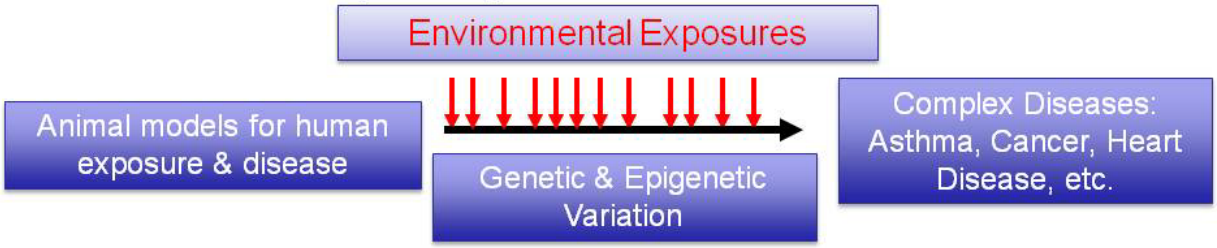
Improved measures of body burden

Linking individual exposure to biology and to disease thru genetics

(Adapted from National Research Council, 1987)

NTP
National Toxicology Program

Host Susceptibility to Environmental Xenobiotics



$$\text{Phenotype} = [G + E + (G \times E)] \times T$$

To determine:

- Population-level range of biological response to exposure related toxicity and disease using mouse models for the human populations
- Genetic and/or epigenetic basis for the MOA
- Identify the causally related mouse genic and/or intergenic sequences for functional validation and identification of human orthologs associated with highly conserved biological pathways

Mouse Models for Human Disease

- Population genetics (inherited & environmental factors)
  - Inter-individual heritable factors associated with genetic susceptibility to disease
  - SNPs, Copy Number Variants (CNV), Epigenetics, and miRNAs
- Hazard Identification and Risk Characterization
  - Using genetic diversity within a test species for exposure assessment
  - Defining boundaries based on variable ranges of response (Human and mouse exposures and outcomes)
- Extrapolation across species
  - Defining MOA (In vitro cell-based & in vivo molecular toxicology)
  - Anchoring MOA to multiple causally related genic & non-genic variants and human orthologs (comparative genetical genomics)

Host Susceptibility Branch

Mission of the HSB is to

(a) develop and test genetically diverse and genetically modified animal models for variable biologic response to toxic agents of public health importance,

(b) determine the genetic and epigenetic basis for the variable biological response to toxic agent exposure, and

(c) identify the mode or mechanistic bases for agent specific associated toxicity that are highly conserved in order to improve the scientific basis for toxicology research and extrapolation between species.

Project Themes

- **The NIEHS/NTP Perlegen Resequencing Project**
- ADME & Toxicogenetics
- Environmental Cardiotoxins
- Aging, Environmental Exposures, and Disease

HSB Scientific Staff (Discipline)	NIEHS /Collaborators (Discipline)
Auerbach, Scott (molecular toxicology)	Dunnick, June K. (toxicology)
Cunningham, Michael (toxicology)	Irwin, Richard (toxicology)
French, John E. (physiology)	Kissling, Grace (biostatistics)
Johnson, Frank (genetics)	Peckham, John (toxicologic pathology)
Stasiewicz, Stanley (biology)	Shockley, Keith (bioinformatics)

NTP
National Toxicology Program

Questions/Comments